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Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial

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SUMMARY

Background Necitumumab is a second-generation, recombinant, human immunoglobulin G1 EGFR antibody. In this study, we aimed to compare treatment with necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone in patients with previously untreated stage IV squamous non-small-cell lung cancer.

Methods We did this open-label, randomised phase 3 study at 184 investigative sites in 26 countries. Patients aged 18 years or older with histologically or cytologically confirmed stage IV squamous non-small-cell lung cancer, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate organ function and who had not received previous chemotherapy for their disease were eligible for inclusion. Enrolled patients were randomly assigned centrally 1:1 to a maximum of six 3-week cycles of gemcitabine and cisplastin chemotherapy with or without necitumumab according to a block randomisation scheme (block size of four) by a telephone-based interactive voice response system or interactive web response system. Chemotherapy was gemcitabine 1250 mg/m^2 administered intravenously over 30 min on days 1 and 8 of a 3-week cycle and cisplatin 75 mg/m^2 administered intravenously over 120 min on day 1 of a 3-week cycle. Necitumumab 800 mg, administered intravenously over a minimum of 50 min on days 1 and 8, was continued after the end of chemotherapy until disease progression or intolerable toxic side-effects occurred. Randomisation was stratified by ECOG performance status and geographical region. Neither physicians nor patients were masked to group assignment because of the expected occurrence of acne-like rash—a class effect of EGFR antibodies—that would have unmasked most patients and investigators to treatment. The primary endpoint was overall survival, analysed by intention to treat. We report the final clinical analysis. This study is registered with ClinicalTrials.gov, number NCT00981058.

Findings Between Jan 7, 2010, and Feb 22, 2012, we enrolled 1093 patients and randomly assigned them to receive necitumumab plus gemcitabine and cisplatin (n=545) or gemcitabine and cisplatin (n=548). Overall survival was significantly longer in the necitumumab plus gemcitabine and cisplatin group than in the gemcitabine and cisplatin alone group (median 11 · 5 months [95% CI 10·4-12·6]) vs 9·9 months [8·9-11·1]; stratified hazard ratio 0·84 [95% CI 0·74-0·96; p=0·01]). In the necitumumab plus gemcitabine and cisplatin group, the number of patients with at least one grade 3 or worse adverse event was higher (388 [72%] of 538 patients) than in the gemcitabine and cisplatin group (333

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[62%] of 541), as was the incidence of serious adverse events (257 [48%] of 538 patients *vs* 203 [38%] of 541). More patients in the necitumumab plus gemcitabine and cisplatin group had grade 3-4 hypomagnesaemia (47 [9%] of 538 patients in the necitumumab plus gemcitabine and cisplatin group *vs* six [1%] of 541 in the gemcitabine and cisplatin group) and grade 3 rash (20 [4%] *vs* one [<1%])· Including events related to disease progression, adverse events with an outcome of death were reported for 66 (12%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group and 57 (11%) of 541 patients in the gemcitabine and cisplatin group; these were deemed to be related to study drugs in 15 (3%) and ten (2%) patients, respectively. Overall, we found that the safety profile of necitumumab plus gemcitabine and cisplatin was acceptable and in line with expectations.

Interpretation Our findings show that the addition of necitumumab to gemcitabine and cisplatin chemotherapy improves overall survival in patients with advanced squamous non-small-cell lung cancer and represents a new first-line treatment option for this disease.

Funding Eli Lilly and Company.

RESEARCH IN CONTEXT

Evidence before this study

In the development of the study design and protocol, we did a systematic review of the published scientific literature. We searched PubMed, with no time restrictions; abstracts of major oncology congresses; and trial websites including ClinicalTrials.gov, for English-language preclinical reports and clinical trials assessing chemotherapy in patients with lung cancer, EGFR therapies in these patients, and the combination of these methods. Search terms for clinical trials of moleculartargeted therapies included "lung cancer" and "EGFR". Clinical data in support of this trial included a phase 1 pharmacological study of necitumumab in patients with advanced solid malignancies that showed necitumumab was well tolerated and had anti-tumour activity at therapeutically relevant trough concentrations. On the basis of our review of the literature and discussions with clinicians, researchers, and regulatory bodies, we postulated that combining chemotherapy with an EGFR-targeted therapy might improve treatment efficacy in patients with advanced squamous non-small-cell lung cancer.

Added value of this study

Ourstudy shows a significant reduction in risk of death and an overall acceptable safety profile in patients who received necitumumab plus gemcitabine and cisplatin. The improvement in overall survival in this patient population compared with those who received gemcitabine and cisplatin chemotherapy alone was supported by a corresponding significant improvement in progression-free survival and a high consistency of the effectsof the treatments in subgroup analyses. We recorded no evidence for a predictive association between an EGFR H-score of 200 or more and survival for necitumumab plus gemcitabine and cisplatin in this setting.

Implications of all the available evidence

The SQUIRE trial design was appropriate forthe first-line treatment of a patient population with squamous non-small-cell lung cancer and can be generalised to clinical practice. The results confirm the benefit of the addition of an EGFR antibody to standard chemotherapy in this setting and represent clinically meaningful progress in the treatment of squamous non-small-cell lung cancer.

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INTRODUCTION

Squamous cell carcinomas account for 30% of non-small-cell lung cancers worldwide.[1] In addition to histopathological differences, the mutational profiles of squamous and non-squamous non-small-cell lung cancers are distinctive, with both of these aspects potentially affecting treatment selection.[2] For patients with squamous non-small-cell lung cancer, although some potentially targetable molecular lesions have been identified in tumours,[1,3] including *PIK3CA* amplification, *FGFR1* amplification, *MET* amplification, and *DDR2* mutation, none of these biomarkers have yet been validated in this setting as predictive for particular targeted therapies, and available first-line regimens have remained essentially unchanged for the past two decades. In general, such regimens comprise a platinum-based doublet of cisplatin or carboplatin combined with gemcitabine, vinorelbine, or a taxane.[1,4] By contrast, for patients with non-squamous non-small-cell lung cancer, the availability of pemetrexed and bevacizumab as components of first-line or maintenance regimens has widened the choice of possible treatments and provided the opportunity to improve overall survival in this patient group.[5-9] Additionally, a few recurring somatic tumour mutations have been described in adenocarcinomas, offering the potential for selective pathway-directed systemic therapy.[10-12] In particular, *EGFR* mutations and *ALK* translocations are predictive of outcome in relation to specific targeted drugs,[13,14] but these mutations are very rare in squamous non-small-cell lung cancer.[1,15] Thus, although clear advances have been made in the first-line treatment of non-squamous non-small-cell lung cancer, especially adenocarcinoma, a substantial unmet need persists to improve outcomes for patients with advanced squamous non-small-cell lung cancer. We note in this context the recent US FDA approval of additional second-line options for patients progressing on or after platinum-based chemotherapy: the PD-1 antibody nivolumab for metastatic squamous non-small-cell lung cancer;[16] and the human immunoglobulin G1 VEGFR-2 antibody ramucirumab, in combination with docetaxel, for treatment of metastatic non-small-cell lung cancer (including that of squamous histology).[17] However, only about half of patients continue to second-line treatment,[18] and neither drug is indicated in the first-line setting.

Most non-small-cell lung cancer tumours express EGFR protein, the high-level expression of which is more common in squamous than in non-squamous disease.[19,20] In the phase 3 FLEX trial,[20] the addition of the chimeric EGFR antibody cetuximab to cisplatin and vinorelbine improved overall survival in the first-line treatment of EGFR-expressing, advanced non-small-cell lung cancer, unselected (adenocarcinoma, squamous cell carcinoma, and other) by histological subtype (hazard ratio [HR] 0·871 [95% CI 0·762-0·9%]; p=0·044). However, the survival benefit was greatest in the subgroup of patients with squamous non-small-cell lung cancer (HR 0·80 [95% CI 0·64-1·00]), but was accompanied by a higher frequency of febrile neutropenia overall.

Necitumumab is a second-generation, recombinant, human immunoglobulin G1 EGFR monoclonal antibody that binds to EGFR with high affinity, competing with natural ligands and thereby preventing receptor activation and downstream signalling. In murine non-small-cell lung cancer xenograft models, the addition of necitumumab to gemcitabine and cisplatin—an established chemotherapy regimen for the first-line treatment of advanced squamous non-small-cell lung cancer[21,22]—resulted in a substantial increase in anti-tumour activity.[23] Our randomised, phase 3 study (SQUamous NSCLC treatment with the Inhibitor of EGF REceptor [SQUIRE]) assessed the efficacy and safety of necitumumab plus gemcitabine and cisplatin as first-line treatment for patients with advanced squamous non-small-cell lung cancer. In parallel, the phase 3 INSPIRE study[24] assessed the efficacy and safety of necitumumab plus pemetrexed and cisplatin as first-line treatment for patients with advanced non-squamous non-small-cell lung cancer.

METHODS

Study design and participants

We did this open-label, multicentre, randomised, phase 3 study at 184 investigative sites in 26 countries (listed in the appendix). The full inclusion and exclusion criteria are provided in the appendix. Briefly, patients aged 18 years or older with histologically or cytologically confirmed stage IV (according to the AJCC Cancer Staging Manual, seventh edition[25]) squamous non-small-cell lung cancer were eligible for enrolment. Other key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate organ function (white blood cell count ≥3000 cells per µL, with an absolute neutrophil count ≥1500 cells per µL, platelets ≥100000 per µL, and haemoglobin ≥9·5 g/dL; total bilirubin ≤1·5x the upper limit of normal [ULN], and aspartate aminotransferase and alanine aminotransferase concentrations ≤5·0xULN in the presence of liver metastases or ≤2·5xULN in the absence of liver metastases and serum creatinine ≤1·2x ULN or a

calculated creatinine clearance >50 mL per min). The availability of archived tumour tissue for the analysis of biomarkers was also an inclusion criterion. Key exclusion criteria were: previous chemotherapy for advanced non-small-cell lung cancer, major surgery in the 4 weeks before randomisation, chest irradiation within the 12 weeks before randomisation, the presence of brain metastases that were symptomatic or needed ongoing treatment with steroids or anticonvulsants, clinically relevant coronary artery disease or uncontrolled congestive heart failure, and National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 grade 2 or worse peripheral neuropathy.

The study was done in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable local regulations. The protocol was approved by the ethics committees of all participating centres and all patients provided written informed consent before study entry.

Randomisation and masking

Patients were randomly assigned (1:1) with a stratified, block randomisation scheme (block size of four) via a telephone-based interactive voice response system or interactive web response system to receive necitumumab plus gemcitabine and cisplatin or gemcitabine and cisplatin alone. Randomisation was done centrally by Pharmaceutical Product Development, LLC (Morrisville, NC, USA), and was stratified by ECOG performance status (0-1 *vs* 2) and geographical region (North America, Europe, Australia *vs* South America, South Africa, India vs eastern Asia). The first dose of study drug was planned to be administered within 7 days of randomisation. Neither physicians nor patients were masked to group assignment because the expected occurrence of acne-like rash—a known class effect of EGFR antibodies—would have unmasked most patients and investigators to treatment. An independent data monitoring committee assessed safety during the study on a regular basis; this committee was an independent multidisciplinary group consisting of five members (three medical oncologists, a drug safety expert, and a biostatistician) with no financial s or other interest in the study.

Procedures

Chemotherapy comprised a maximum of six 3-week cycles of gemcitabine 1250 mg/m^2 administered intravenously over 30 min on days 1 and 8, and cisplatin 75 mg/m^2 administered intravenously over 120 min on day 1. For those assigned to receive it, necitumumab at an absolute dose of 800 mg was given intravenously on days 1 and 8, over a minimum of 50 min and before gemcitabine administration. Antiemetic premedication for gemcitabine and cisplatin was administered according to local practice. Pre-emptive treatment for skin toxicity was allowed only after the first cycle. After the end of chemotherapy, patients who were free of disease progression continued to receive single-agent necitumumab on the same treatment schedule until radiographic documentation of disease progression, the occurrence of toxic effects necessitating cessation, or withdrawal of consent. Dose modifications of chemotherapy or necitumumab were allowed according to protocol-defined criteria (appendix).

We assessed tumour response radiographically according to RECIST version 1·0 criteria[26] at baseline, within 21 days before randomisation, and then every 6 weeks after the first dose of study therapy until radiographic documentation of progressive disease. The appendix provides details of the timing of laboratory and other assessments. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 16·0 and graded with the NCI-CTCAE version 3.0. We assessed patient health status with the Lung Cancer Symptom Scale[27] and the EuroQol-5D.[28] Tumour EGFR protein expression was assessed at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory by immunohistochemistry with the EGFR PharmDx Kit (Dako, Glostrup, Denmark) and assessed independently by two pathologists. The level of EGFR expression was classified by immunohistochemistry score (H-score) on a scale of 0-300, as described previously[29,30]

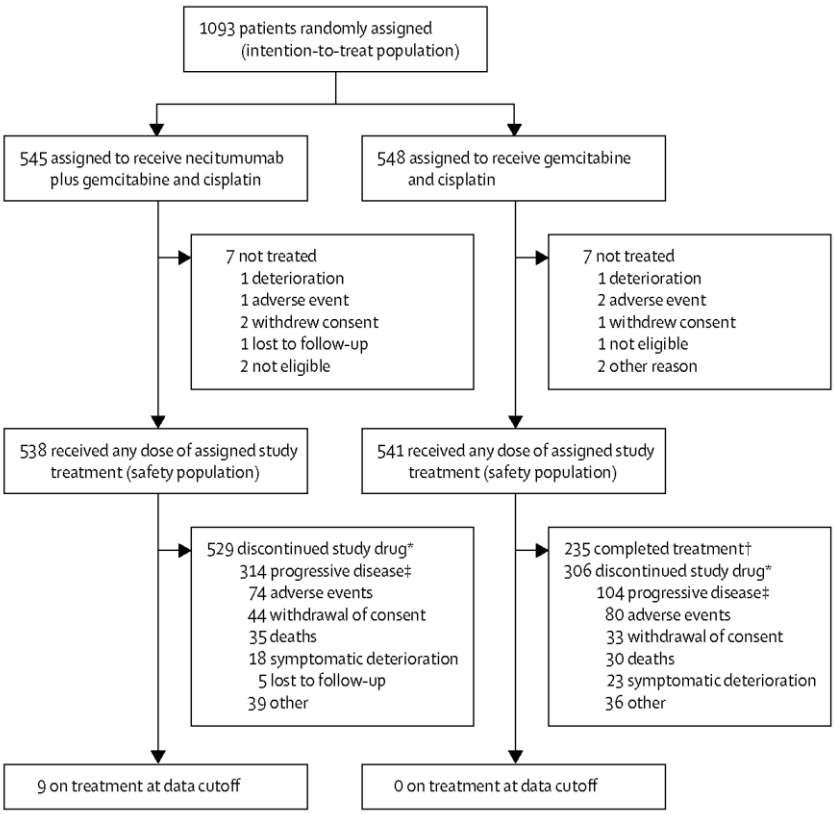
Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause.

Secondary endpoints were progression-free survival, defined as the time from randomisation until the first radiographic documentation of objective progression or death from any cause; objective response, defined as the proportion of patients with a best response of complete or partial response; time to treatment failure, defined as time from the date of randomisation until the date of the first radiographic documentation of progressive disease, death by any cause, discontinuation of treatment for any

reason, or initiation of new anticancer therapy; health status; immunogenicity of necitumumab; safety of necitumumab; and pharmacokinetics of necitumumab.

***Figure*l:Trial profile**



*Primary reasons are listed, †Patients who completed all planned cycles of chemotherapy. ‡Radiologically documented.

Statistical analysis

We used a two-tailed log-rank test at the 0·05 significance level and calculated that enrolment of 1080 patients (with a 5% dropout rate considered) would give 90% power to detect a statistically significant difference of overall survival with an HR for necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone of 0·8, and a calculated improvement in median overall survival from 11·0 months for gemcitabine and cisplatin to 13·75 months for necitumumab plus gemcitabine and cisplatin.[31] We planned to do the final analysis when 844 deaths had occurred.

We assessed efficacy in the intention-to-treat population that included all randomly assigned patients. Safety was assessed in all patients who received at least one dose of study medication and was analysed according to actual treatment received. For the primary and secondary analyses, we estimated overall and progression-free survival using the Kaplan-Meier method[32] and we compared these outcomes between treatment groups using the log-rank test, stratified by the randomisation strata. Overall survival was censored on the last date that the patient was known to be alive. We estimated HRs and 95% CIs for necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin from stratified Cox proportional hazards models. To formally test the proportional hazards assumption, a Cox proportional hazards model was fitted (using the PHREG procedure in SAS) for overall survival with the following predictors: treatment, and an interaction term of treatment and log of event time.

We compared the proportion of patients with an objective response in each treatment group using the Cochran-Mantel-Haenszel test, adjusting for the stratification variables. In the event that a statistically significant result was recorded for the primary endpoint, we planned to use Hochberg's method[33] to adjust for multiplicity of testing in relation to progression-free survival and objective response; if the least significant p value from these endpoints was smaller than 0·05, both null hypotheses could be

rejected to claim significance for both. Otherwise, if the most significant p value was smaller than 0·025, the null hypothesis was to be rejected for this endpoint and the result judged to be statistically significant.

In a preplanned exploratory analysis, we categorised patients into high (H-score ≥200) and low (H-score <200) tumour EGFR expression groups, as previously reported,[29] to investigate whether or not an H-score of 200 or higher was predictive for necitumumab benefit. HR calculations for EGFR expression subgroups were unstratified, and we calculated p values using likelihood ratio tests. We also assessed interactions between treatment groups and EGFR expression subgroups in relation to these endpoints using likelihood ratio tests.

SAS version 9.1.3 was used for data analyses. This study is registered with ClinicalTrials.gov, number NCT00981058.

Role of the funding source

The funder of the study was responsible for data management, commissioning of laboratory investigations, and statistical analysis, and designed the study in conjunction with NT, FRH, LP-A, and MAS (the steering committee investigators). The funder interpreted data in collaboration with the authors and supported development of the report by providing medical writing and editorial assistance. The steering committee had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Table 1: **Baseline characteristics**

	Necitumumab plus gemcitabine and cisplatin (n=545)	**Gemcitabine and cisplatin (n=548)**
Age (years)	62 (32-84)	62 (32-86)
Age group (years)		
<65	332 (61%)	340 (62%)
≥65 to <70	105 (19%)	111 (20%)
≥70	108 (20%)	97 (18%)
Sex		
Male	450 (83%)	458 (84%)
Female	95 (17%)	90 (16%)
ECOG performance status*		
0	164 (30%)	180 (33%)
1	332 (61%)	320 (58%)
2	49 (9%)	47 (9%)
Ethnic origin		
White	457 (84%)	456 (83%)
Asian	43 (8%)	42 (8%)
Black or African-American	5 (<1%)	6 (1%)
All others	40 (7%)	44 (8%)
Smoking history		
Smoker	500 (92%)	495 (90%)
Non-smoker	26 (5%)	27 (5%)
Ex-light smoker	18 (3%)	26 (5%)
Missing	1 (<1%)	0
Geographical region†		
North America, Europe, or Australia	472 (87%)	475 (87%)
South America, South Africa, or, India	30 (6%)	32 (6%)
Eastern Asia	43 (8%)	41 (7%)
Disease histology		
Squamous	543 (100%)	545 (99%)
Other‡	2 (<1%)	3 (<1%)

	Necitumumab plus gemcitabine and cisplatin (n=545)	Gemcitabine and cisplatin (n=548)
(Continued from previous page)		
Number of metastatic organ systems		
0	0	1 (<1%)
1	51 (9%)	50 (9%)
2	193 (35%)	193 (35%)
>2	301 (55%)	304 (55%)
Sites of metastatic disease		
Bone	120 (22%)	131 (24%)
Brain	28 (5%)	30 (5%)
Liver	109 (20%)	117 (21%)
Lung	453 (83%)	453 (83%)
Lymph nodes	431 (79%)	451 (82%)
Peritoneal	20 (4%)	17 (3%)
Pleural	149 (27%)	155 (28%)
Skin	9(2%)	8 (1%)
Soft tissue	23 (4%)	21 (4%)
Other	156 (29%)	146 (27%)
Disease stage at study entry§		
IV¶	543 (100%)	546 (100%)
IIIBwithout malignant pleural effusion||	1 (<1%)	1 (<1%)
Missing	1 (<1%)	1 (<1%)
Previous anticancer therapy		
Surgery	117 (21%)	106 (19%)
Radiotherapy	42 (8%)	46 (8%)
Systemic (adjuvant/neoadjuvant)	23 (4%)	17(3%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *One patient with ECOG performance status 3 was accidentally enrolled and randomly assigned to the gemcitabine and cisplatin group; this patient did not receive treatment, † As recorded on the electronic case report form. ‡Squamous cell histology not confirmed. §According to the American Joint Committee on Cancer (AJCC) Staging Manual edition effective at the time of randomisation. ¶Includes patients with stage IIIB disease with malignant pleural effusion, defined as stage IV in the AJCC Cancer Staging Manual, seventh edition. ||These patients with stage IIIB disease without malignant pleural effusion were enrolled accidentally.

RESULTS

Between Jan 7, 2010, and Feb 22, 2012, we enrolled 1093 eligible patients and randomly assigned them to necitumumab plus gemcitabine and cisplatin (n=545) or gemcitabine and cisplatin (n=548). Seven patients in each group did not receive study treatment, and therefore the safety population comprised 1079 patients (figure 1). The baseline characteristics of the treatment groups were well balanced (table 1); notably, 605 (55%) of 1093 patients had metastases to more than two organ systems and 96 (9%) had an ECOG performance status of 2. Data cutoff for the present analysis was June 17, 2013, at which time 860 (79%) of 1093 patients had died (censoring rate: 233 [21%] of 1093 patients).

The median duration of follow-up was 25·2 months (IQR 19·7-30·5) in the necitumumab plus gemcitabine and cisplatin group and 24·8 months (19·4-31·3) in the gemcitabine and cisplatin group. Exposure to chemotherapy was similar in both treatment groups (appendix). The median number of cycles of both gemcitabine and cisplatin was six (IQR 3-6) in the necitumumab plus gemcitabine and cisplatin group, and five (3-6) in the gemcitabine and cisplatin group. The proportion of patients completing at least six cycles of therapy with gemcitabine was 294 (55%) of 538 in the necitumumab plus gemcitabine and cisplatin group versus 259 (48%) of 541 in the gemcitabine and cisplatin group, and for cisplatin was 286 (53%) of 538 versus 249 (46%) of 541; the median relative dose intensities for gemcitabine were 86% (IQR 75-97) versus 86% (74-96) and for cisplatin were 95% (86-99) versus 95% (86-100), respectively. Patients who continued with necitumumab after the end of chemotherapy (n=275) received a median of four additional cycles of treatment (IQR 2-8). Of the 528 patients who received necitumumab plus gemcitabine and cisplatin and whose serum was analysed for the presence of anti-necitumumab antibodies, 81 (15%) had positive samples at any time during the study

and 15 (3%) had positive samples after treatment. The overall frequency of treatment-emergent antibody positive samples was judged to be too low to allow any further analysis.

Necitumumab had the expected pharmacokinetic characteristics of an immunoglobulin G-type monoclonal antibody. Accumulation of necitumumab drug concentration across cycles was consistent with the previously reported half-life of necitumumab from other studies (data not shown).[34]

Table 2 summarises the efficacy results. Overall survival was statistically significantly better in the necitumumab plus gemcitabine and cisplatin group than in the gemcitabine and cisplatin group (stratified HR 0·84 [95% CI 0·74-0·96], p=0·01). The Kaplan-Meier curves show an early separation in favour of the necitumumab plus gemcitabine and cisplatin group from around 3 months that is maintained for the duration of the study (figure 2A). The Cox proportional hazards model test indicated that no violation of the proportional hazards assumption had occurred.

In the necitumumab plus gemcitabine and cisplatin group, progression-free survival was also statistically significantly improved compared with the gemcitabine and cisplatin group (table 2, figure 2B) and time to treatment failure was also longer than in the gemcitabine and cisplatin group (stratified HR 0·84 [0·75-0·95], p=0·006; table 2). In subgroup analyses of overall and progression-free survival, the necitumumab treatment benefit was reported across most subgroups (figure 3A, 3B). Objective responses were recorded in similar proportions of patients in the two groups Cochran-Mantel-Haenszel p=0·40; table 2). However, disease control was statistically significantly more common in the necitumumab plus gemcitabine and cisplatin group than in the gemcitabine and cisplatin group (Cochran-Mantel-Haenszel p=0·043; table 2). The numbers of patients who received post-study systemic anticancer therapy were similar in the two groups: 258 (47%) of 545 in the necitumumab plus gemcitabine and cisplatin group and 245 (45%) of 548 in the gemcitabine and cisplatin group (appendix).

Tissue samples from 982 (90%) of 1093 patients were evaluable by immunohistochemistry for EGFR protein expression level. EGFR expression was high (H-score ≥200) in 374 (38%) of 982 cases and low (H-score <200) in 608 (62%). We noted that the HR for overall survival for necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone was more favourable in patients bearing tumours with high EGFR expression (HR 0·75 [95% CI 0·60-0·94]) than in those with low EGFR expression (0·90 [0·75-1·07]; figure 4). There seemed to be no difference between high and low H-score groups when assessing progression-free survival (figure 4). For both overall and progression-free survival, interaction tests did not show a significant difference in HRs between the high versus low EGFR expression group, consistent with a discriminatory H-score threshold of 200 not being predictive of a differential necitumumab effect (figure 4, appendix). Assessment of main-effects models using this threshold also did not show significant prognostic associations with overall survival (p=0·67) or progression-free survival (p=0·95; data not shown).

388 (72%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group and 333 (62%) of 541 in the gemcitabine and cisplatin group had one or more grade 3 or worse treatment-emergent adverse events (appendix). Grade 3 or worse adverse events that were more common in the necitumumab plus gemcitabine and cisplatin group than in the gemcitabine and cisplatin group included hypomagnesaemia (47 [9%] of 538 *vs* six [1%] of 541 patients) and rash (20 [4%] *vs* one [<1%] patient, respectively; appendix). The incidence of grade 3 or worse diarrhoea was similar between treatment groups (nine [2%] of 538 vs eight [1%] of 541 patients, respectively).

We recorded adverse events leading to delay or modification of at least one study drug in 321 (60%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group and 312 (58%) of 541 in the gemcitabine and cisplatin group. The most frequent of these events in both groups were blood and lymphatic system disorders (neutropenia, thrombocytopenia, anaemia, and leukopenia), which occurred in 214 (40%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group and 227 (42%) of 541 in the gemcitabine and cisplatin group. Adverse events leading to discontinuation of at least one study drug were reported by 168 (31%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group and by 133 (25%) of 541 in the gemcitabine and cisplatin group. Neutropenia and thrombocytopenia were the most common reasons for treatment discontinuation of any therapy (data not shown). Including events related to disease progression, adverse events with an outcome of death were reported for 66 (12%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group and 57 (11%) of 541 patients in the gemcitabine and cisplatin group (appendix); these were deemed to be related to study drugs in 15 (3%) and ten (2%) patients, respectively. Serious adverse events were reported more frequently in patients in the necitumumab plus gemcitabine and cisplatin group (257 [48%] of 538 patients) than in the gemcitabine and cisplatin

group (203 [38%] of 541).

To further assess safety, adverse events of interest were defined on the basis of the known safety profiles of other EGFR antibodies and previous clinical experience with necitumumab, gemcitabine, or cisplatin (table 3). Events pooled under the categories of skin reactions, rash, hypomagnesaemia, and venous thromboembolic events were reported more frequently (any grade and grade 3 or worse) in the necitumumab plus gemcitabine and cisplatin group than in the gemcitabine and cisplatin group. For example, the incidence of venous thromboembolic events of any grade was 49 (9%) of 538 patients in the necitumumab plus gemcitabine and cisplatin group versus 29 (5%) of 541 patients in the gemcitabine and cisplatin group, whereas the incidence of grade 3 or worse of these events was 27 (5%) versus 14 (3%), respectively. Notably, the rate of fatal venous or arterial thromboembolic events did not differ significantly between treatment groups (<1% in both groups). Overall, the safety profile was generally similar for subgroups of patients aged younger than 70 years and those aged 70 years or older (appendix).

Analyses of health status did not suggest a consistent or compelling difference between the treatment groups. In particular, time to deterioration for the six major symptoms associated with lung malignancies, as measured on the Lung Cancer Symptom Scale, was generally similar between treatment groups, which indicates that the addition of necitumumab to gemcitabine and cisplatin was not associated with deterioration in patient health-related quality of life (appendix).[35]

Table2: **Efficacy endpoints**

	Necitumumab plus gemcitabine and cisplatin (n=545)	**Gemcitabine and cisplatin (n=548)**
Overall survival		
Deaths	418 (77%)	442 (81%)
Median overall survival, months (95% CI)	11·5 (10·4-12·6)	9·9 (8·9-11·1)
1 year overall survival (95% CI)	48% (43-52)	43% (39-47)
2 year overall survival (95% CI)	20% (16-24)	17% (13-20)
Progression-free survival		
Deaths or disease progressions	431 (79%)	417 (76%)
Median progression-free survival, months (95% CI)	5·7 (5·6-6·0)	5·5(4·8-5·6)
3 month progression-free survival (95% CI)	79% (76-83)	73% (68-76)
6 month progression-free survival (95% CI)	45% (40-49)	37% (33-42)
Time to treatment failure		
Events	529 (97%)	528 (96%)
Mediantime,months(95%CI)	4·3 (4·2-4·8)	3·6 (3·3-4·1)
Response		
Best overall response		
Complete response	0	3 (<1%)
Partial response	170 (31%)	155 (28%)
Stable disease	276 (51%)	264 (48%)
Progressive disease	41 (8%)	55 (10%)
Not evaluable	4 (<1%)	12 (2%)
Not assessed	54 (10%)	59 (11%)
Patients achieving an objective response (%; 95% CI)	170 (31%; 27-35)	158 (29%; 25-33)
Patients achieving disease control (%;95%CI)*	446 (82%; 78-85)	422 (77%; 73-80)

Data are n (%) unless otherwise indicated. *Defined as the proportion of patients who had a best response of complete response, partial response, or stable disease (prespecified analysis).

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Figure 2: **Kaplan-Meier estimates of overall and progression-free survival**

(A) Overall survival and (B) progression-free survival in the intention-to-treat population.The stepped appearance of the Kaplan-Meier plot is a function of the strict assessment of response status every 6 weeks. HR=hazard ratio.

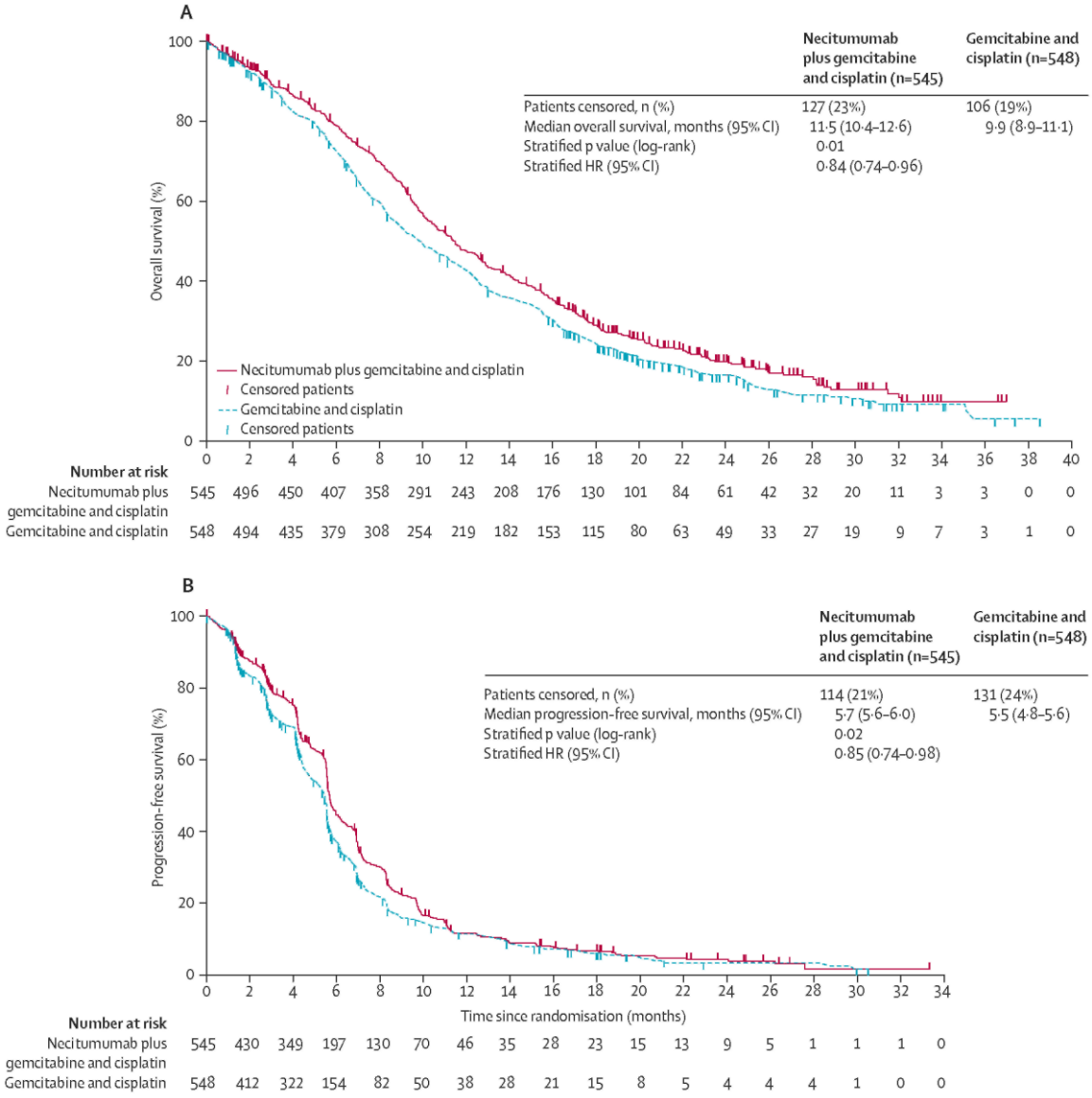

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Figure3: Subgroup analyses

(A) Overall survival and (B) progression-free survival in subgroups defined by baseline characteristics. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. *Stratified HR for intention-to-treat population; unstratified HR for subgroups.

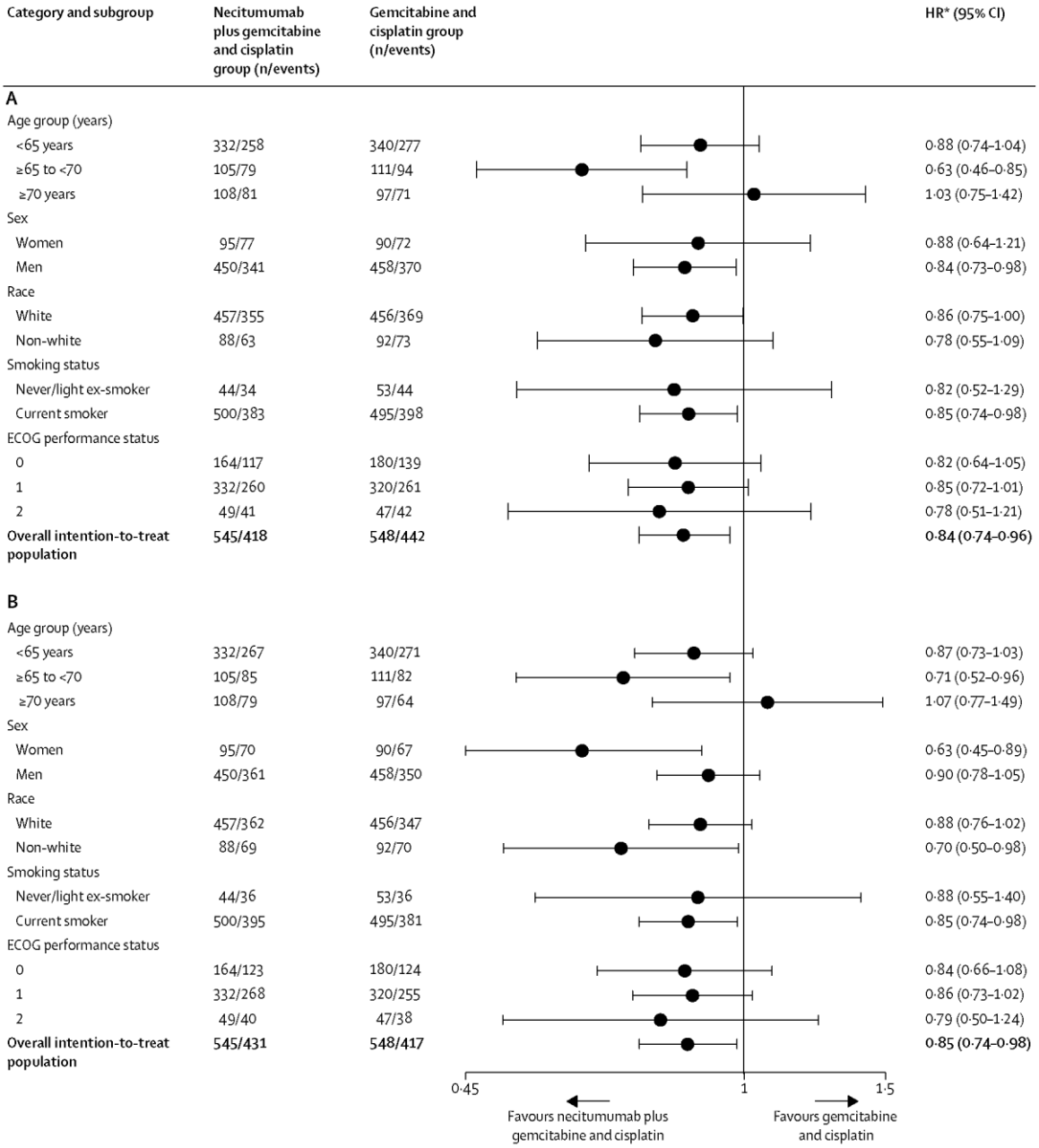

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Figure4 : **Forest plots of overall (A) and progression-free (B) survival in high (H-score ≥200) and low (H-score <200) tumour EGFR expression groups**

HR=hazard ratio. *Stratified HRfor iπteπtioπ-to-treat population; unstratified HRfor H-scores ≥200 and <200.

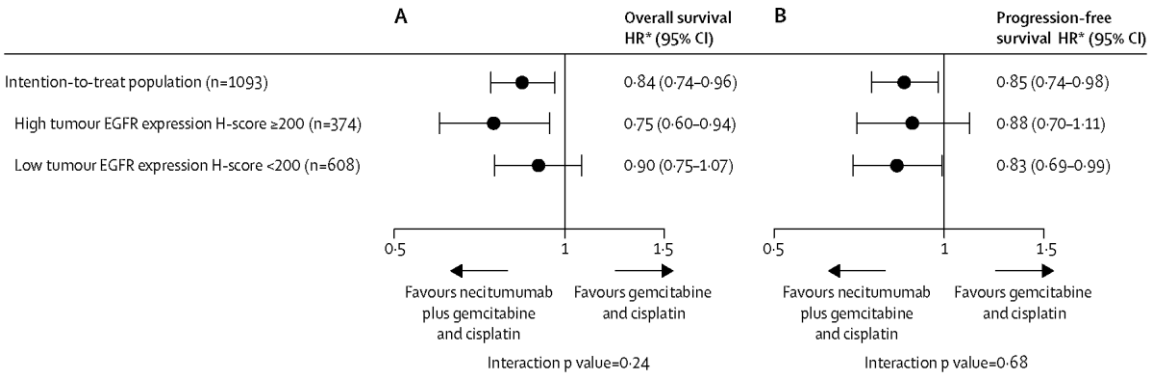

***Table* 3: Adverse events of interest**

	Necitumumab plus gemcitabine and cisplatin (n=538)				Gemcitabine and cisplatin (n=541)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Neutropenia	104 (19%)	97 (18%)	34(6%)	0	99 (18%)	106 (20%)	43 (8%)	0
Febrile neutropenia	2 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)	6 (1%)	1 (<1%)	0
Anaemia	168 (31%)	55 (10%)	2 (<1%)	0	189 (35%)	56 (10%)	3 (<1%)	0
Thrombocytopenia	62 (12%)	38 (7%)	17 (3%)	0	88 (16%)	35(6%)	23 (4%)	0
Diarrhoea	75 (14%)	9 (2%)	0	0	53 (10%)	6 (1%)	2 (<1%)	0
Fatigue	190 (35%)	38 (7%)	1 (<1%)	0	192 (35%)	36 (7%)	2 (<1%)	0
Hypomagnesaemia	118 (22%)	37 (7%)	13 (2%)	0	79 (15%)	6 (1%)	0	0
Skin reactions	380 (71%)	44 (8%)	0	0	61 (11%)	3 (<1%)	0	0
Rash	372 (69%)	38 (7%)	0	0	53 (10%)	2 (<1%)	0	0
Hypersensitivity/infusion-related reaction	6 (1%)	2 (<1%)	0	0	11 (2%)	0	0	0
Conjunctivitis	38 (7%)	2 (<1%)	0	0	12 (2%)	0	0	0
Interstitial lung disease (pneumonitis)	3 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	3 (<1%)	0	0
Arterial thromboembolic events	8 (1%)	13 (2%)	5 (<1%)	3 (<1%)	10 (2%)	8(1%)	2 (<1%)	1 (<1%)
Venous thromboembolic events	22 (4%)	19 (4%)	7 (1%)	1 (<1%)	15 (3%)	5 (<1%)	8 (1%)	1 (<1%)

Data are n (%). The table shows adverse events of interest possibly related to study treatment, according to either composite categories or preferred terms (febrile neutropenia and diarrhoea only). Adverse events of grade 1-2 in 10% or more of patients in either treatment group, or grades 3-5 in one or more patients in either treatment group, are presented in the appendix.

DISCUSSION

Our findings show that the addition of necitumumab to gemcitabine and cisplatin was associated with a statistically significant improvement in overall survival in patients with advanced squamous non-small-cell lung cancer. This treatment effect was supported by a corresponding statistically significant improvement in progression-free survival. In this broad patient population, which is typical of one seen in clinical practice, outcome improvements were recorded across major subgroups at a similar level of magnitude. Notably, a necitumumab benefit was apparent for patients with an ECOG performance status of 2. Although the subgroup analyses provided no evidence that patients aged 70 years or older benefited from the addition of necitumumab to gemcitabine and cisplatin, we cannot exclude the possibility that this is a chance finding. The safety profile of necitumumab combined with gemcitabine and cisplatin was acceptable and consistent across patient subgroups, including in elderly patients.[36]

These findings are consistent with results from previous clinical trials and a meta-analysis of individual patient data from four randomised studies in which chemotherapy plus the chimeric EGFR antibody cetuximab, which interacts with a similar EGFR epitope to necitumumab,[37] was compared with chemotherapy alone in patients with non-small-cell lung cancer.[38] The meta-analysis showed a clear overall survival benefit for cetuximab in patients with squamous non-small-cell lung cancer (HR 0·77 [95% CI 0·64-0·93]). By contrast, in the parallel phase 3 INSPIRE trial,[24] the addition of necitumumab to a first-line pemetrexed and cisplatin treatment regimen did not improve overall survival in patients with non-squamous non-small-cell lung cancer.

The early divergence of the Kaplan-Meier plots for overall survival (at around 3 months) and progression-free survival (at around 2 months) in our study suggests a clear benefit of necitumumab, which starts during the chemotherapy phase of treatment. However, the study design does not allow us to ascertain the benefit of the continued administration of necitumumab after the end of chemotherapy. Since roughly equal numbers of patients in the treatment groups received post-study systemic anticancer therapy and in view of the fact that the type of post-study systemic anticancer therapy also seemed to be reasonably balanced between the treatment groups, our data suggest that the overall survival benefit in the necitumumab plus gemcitabine and cisplatin group is based on the addition of necitumumab to chemotherapy, rather than an imbalance in post-study systemic anticancer therapy.

The addition of necitumumab to gemcitabine and cisplatin was associated with an increased occurrence of grade 3 or worse adverse events. This finding was especially apparent in relation to hypomagnesaemia and skin reactions, which are manageable side-effects typically associated with EGFR antibodies.[39,40] Also in line with expectations for such agents when combined with platinum-based chemotherapy[41] venous thromboembolic events were more common in the necitumumab plus gemcitabine and cisplatin group than in the control group. However, importantly, the incidence of fatal thromboembolic events did not differ between treatment groups. Moreover, no relevant increase in the incidence of toxicities typically associated with chemotherapy occurred in the necitumumab plus gemcitabine and cisplatin group. By contrast with data from the FLEX trial,[20] febrile neutropenia was reported rarely and the incidence was essentially balanced between treatment groups, as was that of grade 3 or worse neutropenia. In line with expectations for a human antibody[42,43] no increases in the overall incidence of hypersensitivity or infusion-related reactions associated with the administration of necitumumab were reported.

High-level expression of EGFR protein in advanced non-small-cell lung cancer (tumour H-score ≥200) might

be predictive for the overall survival benefit associated with the addition of cetuximab to first-line chemotherapy[29] In a prospectively planned analysis, we therefore explored whether or not an H-score of 200 or higher was of predictive value in patients receiving necitumumab plus gemcitabine and cisplatin. We noted that interaction test p values for treatment by EGFR expression level for both overall and progression-free survival were not significant. These findings are consistent with a discriminatory H-score of 200 not being of predictive value. Notably, a discriminatory EGFR H-score of 200 was also not predictive for treatment efficacy in patients with non-squamous non-small-cell lung cancer who received necitumumab plus pemetrexed and cisplatin.[24] Exploratory analyses in this study for potential associations between efficacy and another potential EGFR pathway or non-small-cell lung cancer biomarker, or the early occurrence of skin rash are ongoing and will be reported elsewhere.

In conclusion, to the best of our knowledge, SQUIRE is the first trial of first-line treatment for advanced squamous non-small-cell lung cancer to show that the addition of a targeted agent to a platinum-based doublet improves survival. These efficacy data and the acceptable safety profile of necitumumab suggest a favourable benefit-to-risk ratio for this combination treatment.

Contributors

NT was a member of the study steering committee and contributed to data analysis and interpretation, and drafting, review, and approval of the report. FRH was a member of the study steering committee and contributed to planning, study design, data interpretation, and drafting, review, and approval of the report. TEC contributed to data and interpretation; drafting, review, and approval of the submitted report; and the decision to submit for publication. AS, RR, RKG, GL, AK, KP, and MR contributed to drafting, review, and approval of the report. AVL, MD, BB, and CS contributed to patient recruitment, data collection, and drafting, review, and approval of the report. HD and SN contributed to data

analysis and interpretation, and drafting, review, and approval of the report. AK-L contributed to patient recruitment, data collection, and final approval of the report. RK was a member of the steering committee for the study and contributed to study design, data analysis, data interpretation, and drafting, review, and approval of the submitted report. LP-A was a member of the steering committee for the study and contributed to study design; patient recruitment; data collection, analysis, and interpretation; and drafting, review, and approval of the report. MAS was a member of the steering committee for the study and contributed to drafting, review, and approval of the report.

Declaration of interests

NT has received personal fees from Lilly during the conduct of the study and personal fees from Multiple, outside the submitted work. FRH's laboratory has received a grant from Lilly-ImClone for doing biomarker studies related to this clinical trial, and he has participated in advisory boards for Eli Lilly and Company. FRH has also received grants from the University of Colorado during the conduct of the study, and from Lilly-ImClone for consultancy and service on advisory boards outside the submitted work. TEC has received personal fees from Eli Lilly and Company, Merck, Bristol-Myers Squibb, Amgen, Roche, Pfizer, Novartis, Sandoz, Bayer, Vifor Pharma, Janssen, and Merck Sharp and Dohme, outside the submitted work. MD has received personal fees from Eli Lilly and Company, Hoffmann La-Roche, Boehringer Ingelheim, Pfizer, Amgen, Novartis, GlaxoSmithKline, and AstraZeneca, outside the submitted work. RR has received personal fees from Eli Lilly and Company, Boehringer Ingelheim, Merck Sharp and Dohme, and Roche, outside the submitted work. KP has received personal fees from Eli Lilly and Company, outside the submitted work. CS has received grants from Eli Lilly and Company during the conduct of the study, and a speaker's fee from Eli Lilly and Company, outside the submitted work. MR has received personal fees from Hoffmann-La Roche, Eli Lilly and Company, Merck Sharp and Dohme, BMS, AstraZeneca, Pfizer, Boehringer Ingelheim, and Novartis, outside the submitted work. HD, SN, AK-L, and RK are employees of Eli Lilly and Company. LP-A has received honoraria from Eli Lilly and Company. AVL, AS, RKG, BB, GL, AK, and MAS declare no competing interests.

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